PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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Association of Representatives
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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)* 19.06.2006 21.06.06

Applicant's or agent's file reference
P1744PC00

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/000339	19.01.2004	19.01.2004

Applicant
ADVANCED IN VITRO CELL TECHNOLOGIES, S.L. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Moreno, R Tel. +49 89 2399-2658

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1744PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/000339	International filing date *(day/month/year)* 19.01.2004	Priority date *(day/month/year)* 19.01.2004
International Patent Classification (IPC) or national classification and IPC INV. C12N5/06 C12N9/12		
Applicant ADVANCED IN VITRO CELL TECHNOLOGIES, S.L. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.07.2005	19.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wimmer, G Telephone No. +49 89 2399-7347

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/000339

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-26 as originally filed

   Sequence listings part of the description, Pages

   1-7 as originally filed

   Claims, Numbers

   1-13 filed with telefax on 03.02.2006

   Drawings, Sheets

   1/3-3/3 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	12, 13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☒ table(s) related to the sequence listing

   b. format of material:

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment* on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

Re Item V

Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability.

Reference is made to the following documents (the document numbering corresponds to their order of citation in the international search report):

D1: GOMEZ-LECHON M J ET AL: "Human hepatocytes as a tool for studying toxicity and drug metabolism." CURRENT DRUG METABOLISM, vol. 4, no. 4, August 2003 (2003-08), pages 292-312, XP002292149 ISSN: 1389-2002

D2: MCGINNITY D F ET AL: "Predicting drug pharmacokinetics in humans from in vitro metabolism studies" BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 29, no. 2, May 2001 (2001-05), pages 135-139, XP002292150 ISSN: 0300-5127

D3: BRIMER C ET AL: "Creation of polarized cells coexpressing CYP3A4, NADPH cytochrome P450 reductase and MDR1/P-glycoprotein" PHARMACEUTICAL RESEARCH 2000 UNITED STATES, vol. 17, no. 7, 2000, pages 803-810, XP002292151 ISSN: 0724-8741

D4: BORT ROQUE ET AL: "Hepatic metabolism of diclofenac: Role of human CYP in the minor oxidative pathways" BIOCHEMICAL PHARMACOLOGY, vol. 58, no. 5, 1 September 1999 (1999-09-01), pages 787-796, XP002292152 ISSN: 0006-2952

D5: ARORA V ET AL: "PHOSPHODODIAMIDATE MORPHOLINO ANTISENSE OLIGOMERS INHIBIT EXPRESSION OF HUMAN CYTOCHROME P450 3A4 AND ALTER SELECTED DRUG METABOLISM" DRUG METABOLISM AND DISPOSITION, WILLIAMS AND WILKINS., BALTIMORE, MD, US, vol. 30, no. 7, 1 July 2002 (2002-07-01), pages 757-762, XP008005096 ISSN: 0090-9556

D6: CASTELL J V ET AL: "Adenovirus-mediated gene transfer into human hepatocytes: Analysis of the biochemical functionality of transduced cells" GENE THERAPY, vol. 4, no. 5, 1997, pages 455-464, XP002292153 ISSN: 0969-7128

In addition to the documents listed in the International Search Report, reference is made to the following document:

D7: Özen and Korkmaz: "Modulatory effect of Urtica dioica L. (Urticaceae) leaf extract on biotransformation enzyme systems, antioxidant enzymes, lactate dehydrogenase and lipid peroxidation in mice." PHYTOMEDICINE, Vol. 10, No. 5, June 2003, pages 405-415

Novelty under Art. 33(2) PCT.

1) Numerous cellular models for the investigation of drug biotransformation and metabolic idiosyncrasy have been described in the prior art; a variety of documents describes the provision of p450-reductase expressing cell lines of hepatic or other origin, which had been transfected with CYP expression vectors (D1-D4); in particular, transduction by adenoviral vectors had been suggested and shown (D1, D3, D6).

   The documents cited in the Search Report describe hepatic cells transduced with one biotransformation enzyme (e.g. D1), and do not explicitly point to transduction with more than one; novelty of claims 1-11 is therefore formally acknowledged.

2) Document D3 describes adenoviral transduction of various cell lines (albeit not of hepatic origin) with more than one vector encoding Phase I drug biotransformation enzymes, namely CYP3A4 and NADPH p450 reductase, and discloses the investigation of drug biotransformation therewith. In this, D3 discloses subject-matter of claims 12 and 13, which consequently lack novelty.
   The applicant had argued p450 reductase not to be a Phase I or Phase II enzyme; however, this allegation was without basis. On the contrary, NADPH p450 reductase is commonly known in the art as a Phase I enzyme (see e.g. D7, pg. 406, left col., and many others).

Inventive Step under Art. 33(3) PCT.

3) For subject-matter of claim 1 and 9, e.g. D3 can be taken as the closest prior art. In contrast to claimed subject-matter, D3 describes the experiments in renal and colon cancer cells. The problem to be solved was therefore the provision of alternative cellular sources.

   The prior art however describes cells of hepatic origin to be preferable for drug bioconversion studies (D1, D2, D4, D5). In trying to solve the technical problem, the skilled person would therefore preferably choose cells of hepatic origin as alternatives to the cells of D3, and arrive at subject-matter of present claims 1-11, which

consequently lack inventive activity.

4) The applicant viewed D1 to be closest prior art. However also in the view of this, no inventive step can be identified. D1 describes adenoviral transduction of hepatic cells is described with one biotransformation enzyme, however makes clear that the simultaneous expression of several, in the best case all, xenobiotic-metabolizing enzymes in hepatic cell lines is preferable (pg. 307).
While D1 also points to experiments which achieve at least expression of multiple CYP isoforms by transduction with transcription factors, the skilled person would routinely also consider a more trivial solution, namely transduction with several vectors expressing different drug metabolizing enzymes. In this, again, he would arrive at presently claimed subject-matter.

Re Item VII.

During the international procedure, the applicant considered NADPH p450 reductase not to be a Phase I or Phase II drug transformation enzyme, although the prior art lists it as such, and although it is also listed as such an enzyme in the application itself (as "cytochrome c reductase"). Therefrom, it is evident that the terms "a Phase I drug biotransformation enzyme" and "a Phase II drug biotransformation enzyme" are unclear, and more specific terms should be used.